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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
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Esther H. CHANG *et al.*) Examiner: Dave Trong Nguyen
)
Serial No. **09/601,444**) Group Art Unit: 1632
)
Filed: **January 4, 2001**)

For: **TARGETED LIPOSOME GENE DELIVERY**

RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

On March 26, 2002, the Patent Office issued a Restriction Requirement on the claims of the present application (Paper 8). The Patent Office has concluded that the application encompasses seven distinct inventions:

Group I (claims 1-12, 29, 30, 38, 39, and 49-50), drawn to a liposomal complex comprising a virus, a cell-targeting ligand and a liposome, and a first method of using the complex for providing a therapeutic agent to any cell;

Group II (claims 13-28, 31-37, 40, 41-50 and 63-70), drawn to a liposomal complex of less than 100 nm comprising a cell-targeting ligand, a liposome and a therapeutic agent, the first method of providing the therapeutic agent to a target cell, and a method of making a liposomal complex of less than 100 nm;

Group III (claims 40 and 41-50), drawn to method of using a liposomal complex of less than 100 nm comprising a cell-targeting ligand, a liposome and a therapeutic agent for delivering the agent to a cell of interest;

Group IV (claims 63-70), drawn to a method of making liposomal complexes of less than 100 nm comprising a cell-targeting ligand and a liposome;

Group V (claims 51, 58-62), drawn to a second method of treating cancer by using a liposomal complex comprising a virus, a cancer cell-targeting ligand, a therapeutic nucleic acid molecule, and a liposome;

Group VI (claims 52-62), drawn to a second method of treating cancer by using a liposomal complex comprising a cell targeting ligand, a therapeutic nucleic acid molecule, and a liposome, wherein the complex has a mean diameter of less than about 100 nm; and

Group VII (claims 13-17, and 19-28), drawn to a third method of using a liposomal complex comprising a cell-targeting ligand, a diagnostic agent, and a liposome, wherein the complex has a mean diameter of less than 100 nm, for delivering the diagnostic agent to a cell.

In support of this grouping of the claims, the Office Action recites the requirement of PCT Rule 13.1 and PCT Rule 13.2. Applicants respectfully point out to the Examiner that this is a United States application, and not a PCT application, and thus the standards for preliminary examination of an international application under the PCT rules are not the correct standards to apply. The Manual of Patent Examining Procedure (MPEP) states that

> "Under the statute an application may properly be required to be restricted to one or more claimed inventions only if they are able to support separate patents, and they are either independent (MPEP § 806.04 - § 806.04(i)) or distinct (MPEP § 806.05 - § 806.05(i))."

MPEP § 803. The present claims have not been shown to be either independent, or distinct under the definitions of 35 U.S.C. 121: to be independent, there must be no disclosed relationship between two or more subjects disclosed, such that they are "unconnected in design, operation, or effect" (MPEP § 801 (Independent)); to be distinct, two or more subjects that are related as, for example, product and process of manufacture, must be "capable of separate manufacture, use, or sale as claimed." MPEP § 801 (Distinct). The standards under PCT Rules 13.1 and 13.2 applied

by the Patent Office, do not meet these criteria.

"Examiners must provide reasons and/or examples to support conclusions, but need not cite documents to support the requirement in most cases." MPEP § 803 (Guidelines). "If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits..." MPEP § 803. For purposes of the initial requirement "a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classifications, separate status in the art, or a different field of search as defined in MPEP § 808.02." MPEP § 803 (Guidelines). The Patent Office has not shown or explained that the alleged separate inventions fall into separate classifications, have a separate status in the art, or would require different fields of search, and in fact they do not. The Patent Office has completely failed to meet its burden to show that the claims require restriction.

However, even assuming for the sake of argument that the PCT standards were to apply to the present application (which they do not), these rules do not require division into seven inventive concepts. Under 37 C.F.R. Section 1.475(b)(3), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn to "a product, a process specially adapted for the manufacture of the said product, and a use of the said product." Under the Examiner's own definition of the claims, there are, at most, two groups of claims: 1) those drawn to a liposomal complex comprising a virus, a cell-targeting ligand in a liposome, and methods of using the complex (Groups 1 and 5 set forth in Paper 8), and 2) claims drawn to a liposomal complex of less than 100 nm comprising a cell-targeting ligand, a liposome and a therapeutic agent, methods of providing the therapeutic agent to a target cell, and methods for making the liposomal complex of less than 100 nm (encompassing Groups 2-4 and 6-7 of the grouping in Paper 8).

Group V falls completely within the scope of Group I, because it simply specifies cancer

as a condition to be treated, a cancer cell-targeting ligand as the cell-targeting ligand, and a therapeutic nucleic acid molecule as the therapeutic agent. There simply is no distinction between a "first" and a "second" method of use under United States law that requires restriction of these claims, and the Patent Office has pointed to no authority to support such a distinction. Group III falls within the scope of Group II because the Patent Office has not defined it any differently than the methods encompassed within Group II. Group IV falls within the scope of Group II, as the claims therein are directed towards methods of making liposomal complexes of less than 100 nm, and thus represent a process specially adapted for the manufacture of that product in accordance with 37 C.F.R. Section 1.475(b)(3). Group VI falls within the scope of Group II, as it simply defines cancer as the condition to be treated, a cancer cell-targeting ligand as the cell-targeting ligand, and a therapeutic nucleic acid molecule as the therapeutic agent, making it a species of the methods contained in Group II. Group VII falls within Group II for the same reason. The distinction between a diagnostic and a therapeutic agent is immaterial, in that the compositions and process for manufacture are the same in both embodiments, the only difference lying in they types of agents that can be used in the two embodiments (and in many instances, the identical agent can be used in both -- e.g., radiopharmaceuticals). The methods of use are exactly the same, with only the additional step of detecting the diagnostic agent after targeting in the diagnostic embodiment.

This closer grouping of the claims into two, rather than seven, groups is further supported by the fact the claims stated as comprising Group II completely overlap the claims stated as comprising Groups III, IV, VI and VIII, and the only distinction between Groups I and V is the baseless distinction between a "first" and a "second" use. The Patent Office has presented no more than a rote recitation that Groups I-VII are drawn to multiple distinct inventions. The explanation provided by the Patent Office does not provide any grounds for distinguishing between several of the groups: Groups II-VII are stated in conclusory fashion as being "drawn to

multiple distinct processes of use and/or multiple distinct products that do not share the same inventive concept as in Group I;" the special feature of Group II is stated in conclusory fashion as being a liposomal complex having a mean diameter of less than 100 nm, while Groups II-VI are all considered together as reciting "a distinctly named method comprising materially distinct methods that would generate distinct functions and effects." The Examiner has provided no explanation of how or why the methods are distinct, or generate distinct functions and effect. In fact, as stated above, the methods fall, at most, into two groups: those employing a liposomal complex with a virus, and those employing a liposomal complex of a mean diameter less than 100 nm. The methods directing toward treatment of cancer are specific embodiments of the more generic method claims in each group, and therefore do not represent distinct inventions. For all of the foregoing reasons, Applicants traverse the restriction requirement, and believe that it is improperly applied.

Applicants propose the following alternative grouping of claims:

Group I (claims 1-12, 29, 30, 38, 39, 47-51, and 58-62, drawn to a liposomal complex comprising a virus, a cell-targeting ligand and a liposome, in methods of using these complexes (claims 47-50 are included in this group only to the extent that they depend from claim 39).

Group II (claims 13-28, 31-37, 40-50, and 63-70, drawn to a liposomal complex of less than 100 nm comprising a cell-targeting ligand, a liposome and a therapeutic agent, and methods of providing the therapeutic agent to a target cell, and a process specially adapted for the manufacture of that product (claims 47-50 fall within this group only to the extent that they depend from claim 40).

Under this alternative grouping of claims, Applicants elect Group II for prosecution. If this alternative grouping is not accepted, Applicants elect, with traverse, Group II of the original grouping of the claims proposed by the Patent Office.

With regard to the requirement for an election of species for prosecution, Applicants

traverse this requirement. The Patent Office has provided no basis whatsoever to support the necessity of an election of species, and the conclusory explanation provided contradicts both PCT and U.S. rules and practice. Typically, and election of species is required if it will streamline the search or examination process. In the present case, an election of species would do neither. It would not alter the scope of the search, nor would it alter the issues that would have to be addressed during examination. The Patent Office again points to PCT Rules 13.1 and 13.2 as a basis for the requirement of an election of species. Not only are these rules and the standards set forth therein inapplicable to a United States patent application, they do not even mandate an election of species. PCT Rules 13.1 and 13.2 relate to unity of invention. By definition, once an election has been made pursuant to a restriction requirement, the claims all relate to the same invention. It is thus contradictory to then again attempt to define the elected claims as covering different inventions, and PCT Rules 13.1 and 13.2 would not even apply, even if this were a PCT application.

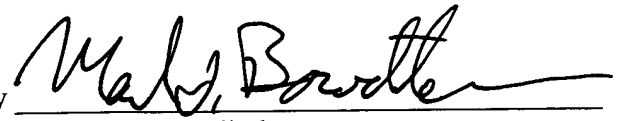
Applicants disagree with the Patent Office's assertion that "none of the listed species as indicated above share a substantial common structure with respect to one another," Paper 8 at 5, because in fact, all of the claims share substantial common structures, i.e., a liposome, a cell-targeting agent, a mean diameter of less than 100 nm (or the inclusion of a virus), and a therapeutic agent. For these reasons Applicants traverse the requirement for an election of species. If this traversal is not accepted, applicants elect for prosecution the embodiment of A) a tumor cell targeting ligand, C) a therapeutic nucleic acid, D) a liposome mean diameter of about 30 to 75 nm, and E) a ratio of 0.1 to 50 nM liposomes per 1.0 μg nucleic acid. No election under category B (virus) is required, as the election under either grouping of the claims excludes the virus embodiment.

Conclusion

Applicants believe that the restriction requirement is improper, and elect with traverse

Group II set forth in Paper 8. Applicants propose as an alternative a two-way restriction, and elect Group II of this alternative grouping for prosecution. Applicants believe that the requirement for an election of species is improper. Applicants therefore traverse this requirement, though an election with traverse has been made.

Respectfully submitted,

By 

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